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## Claim

1. Pathological improvement food composed chiefly of indigestible polysaccharides and having restricted addition of protein components, which contains trace metal, vitamin and/or fat as required.

[0001]

(TECHNICAL FIELD)

This invention relates to food suitable for improving clinical conditions of patients particularly with kidney failure or hepatic failure, and more particularly to pathological improvement food capable of being used for preventing or retarding a transition to hemodialysis treatment in kidney failure or decreasing the number of implementation of the hemodialysis therapy and preventing or lessening occurrence of accompanying hyperammonemia in hepatic insufficiency.

[0002]

(BACKGROUND ART)

(non patentic article 1) Wrong, O. M. & Vince, A.: Proc. Nutr. Soc., 43, pp. 77-86 (1984))

[0003]

There has been so far known that dietary fiber or nonfibrillary hydroscopic carbon has a function of increasing the excretion amount of nitrogen into feces without digesting dietary fiber or non-fibrillary hydraulic carbon in the small intestine of the human or animal. This is disclosed in, for example, Sealock, R. R., Basinski, D. H. & Murlin, J. R.: J. Nutrition, 22, 589-596 (1941); Mason, V. C. & Palmer, R. M.: Proc. Nutr. Soc., 32, 82A, 83A (1973); Weber, F. L. Gastroenterology: 77, 518-523 (1979); and Stephen, A., M. & Cummings, J. H.: Proc, Nutr. Soc., 38, 141A (1979).

[0004]

For the meanwhile, it has known that 40% to 70% of nitrogen in the feces are derived from fungal protein within intestinal bacteria, which makes use of ammonia produced by decomposition of urea secreted into the intestine to convert the fungal protein. (See Wrong, O. M. & Vince, A.: Proc. Nutr. Soc., 43, pp. 77-86 (1984))

[0005]

However, there has been no attempt to lowering concentration of urea in the blood in the presence of kidney failure by positively using the urea secreted into the intestine for of fungal protein synthesis of the intestinal bacteria in the intestine.

[0006]

The medical guideline recommended by Japanese Society of Nephrology provides restriction of protein intake (0.5 to 0.6 g/kg body weight) for preventing increase of urea nitrogen in the blood (Blood Urea Nitrogen; BUN) of a renal failure patient ("Lifestyle guidance and dietary advice for patients with renal disease" compiled by Japanese Society of Nephrology). In addition to the restriction of protein intake, ingestion of quality protein having high biological value (such as animal protein, fishery product, whole egg, etc.) is recommended.

[0007]

To accomplish this purpose, low-gluten wheat is recommended as kidney failure diet, and therefore, there have been developed a good deal of low-protein food

of high-biological value. Further, various dietary supplements and elemental diets containing essential amino acid in a balanced manner have been devised and used.

[0008]

Although high-protein food of high-biological value is recommended for patients with hepatic failure, high-caloric elemental diets containing branched-chain amino acids (valine, leucine and isoleucine) have been devised and used for hepatic disease, because such amino acids provide promotion of insulin secretion and suppression of formation of tryptophan-derived serotonin or other brain amines by being antagonistic to tryptophan with respect to blood-brain barrier to prevent hepatic coma and cause awakening, and arginine contained in the amino acids activates urea cycle.

[0009]

However, the aforesaid diets are mere food or enteral nutrient having a function of decreasing the supply of low-molecular-weight nitrogen-containing compounds such as urea and ammonia or raise hopes for producing symptomatic improvement through the provision high biological value protein or food composed of amino acid at an appropriate ratio of concentration designed in mixture. However, these diets do not fulfill the purpose and function of decreasing BUN since excretion of ingested nitrogen-containing compounds to the outside of the body through the route other than the principal metabolic excretion system or peripheral route.

[0010]

As a result, when the low-molecular-weight nitrogen compounds such as urea derived from protein and amino acid in the diet are accumulated in the blood beyond the filtering ability of the kidney or a renal failure patient, the nitrogen compounds will be discharged outside of the body by hemodiafiltration.

[0011]

Besides the dietetic treatment as noted above, there have been often used medicinal agents such as activated charcoal and cation-exchange resin for absorbing or inactivating ammonia drawn into the intestine to discharge or remove the ammonia as feces so as to decrease the blood ammonia level in the patient with hepatic failure.

[0012]

There have been the following guidelines of alimentary therapy for accomplishing the purposes described above.

[0013]

(1) Quantitative restriction and qualitative enrichment of protein:

It is recommendable to quantitatively restrict the intake of protein and qualitatively enrich the quality of protein in order for reducing the burden of nitric metabolite and preventing decrease in kidney function. In general, low-protein diets (0.6 g/kg body weight for kidney failure, and 1.2 to 1.5 g/kg body weight for hepatic failure) bring about an effect of slowing the deterioration in kidney failure or hepatic failure. Since the dietary treatment should extend over a long period of time, it is



necessary to select the diets of high protein value (protein score) so as to regulate the balance of essential amino acids (“Lifestyle guidance and dietary advice for patients with renal disease” compiled by Japanese Society of Nephrology, Tokyoigakusha (1998), and “Nutritional diagnostics of liver disease/Liver disease and nutritional therapy”, Akiharu Watanabe and Misako Okita, Dai-ichi Shuppan Publishing Co., Ltd., pp. 53–68 (1992)).

[0014]

(2) Sufficient supply of dietary energy

It is thought that 35 kcal/kg of daily energy is appropriate and daily energy intakes of 1800 to 2000 kcal are recommended. (“Lifestyle guidance and dietary advice for patients with renal disease” compiled by Japanese Society of Nephrology, Tokyoigakusha (1998), and “Nutritional diagnostics of liver diseases/Liver disease and nutritional therapy”, Akiharu Watanabe and Misako Okita, Dai-ichi Shuppan Publishing Co., Ltd., pp. 53–68 (1992))

[0015]

(3) Sodium chloride (NaCl) should be restricted in a complication of anasarca and high-blood pressure: If non anasarca and kept the urine volume, NaCl restriction 7–10 g/day, if the anasarca or high blood pressure, should be restricted to 6–7 g, if the anasarca or high blood pressure, it should be restricted under 5 g. But overloaded restriction will be decrease the plasmas and lower the renal sufficient. (Japanese Society of Nephrology, Educational guidance for kidney disease, Educational guideline for feeding, Tokyo Igakusha; 1998)

[0016]

(4) Potassium should be restricted in causing hyperkalemia.

[0017]

(5) Water intake should be restricted with salt when developing signs of anasarca, whereas dehydration requires attention in general.

[0018]

It is generally important to satisfy the quantity and balance of required essential amino acids by low protein diets.

[0019]

Under the conventional technology, it is necessary to give foods of high-biological value and having low total content of nitrogen to a patient with renal failure so as to reduce protein intake, which foods are prepared in such a manner that the proportion of better protein in the foods is increased for improving the quality of protein intake and reducing the total content of nitrogen or by using amino acids, especially, essential amino acid compounds having desirable relative proportions of the amino acids. However, when the concentration of low-molecular-weight nitrogen-containing compounds in the blood surpasses the renal filtration capability, the patient must undergo a hemodialysis treatment.

[0020]

The hemodialysis treatment requires the patient to attend a hospital three or four times a week and have therapy three to five hours on attending occasions. Large temporal, financial and psychological burdens will be exerted on the patient undergoing the hemodialysis treatment, resulting in a major detriment at the individual and social levels.

[0021]

The medicine using the hemodialysis treatment for discharging the low-molecular-weight nitrogen-containing compounds from the blood will impose not only tremendous temporal, financial, physical and psychological burdens upon the patient, but also create more problems such as a large social burden of medical costs covered by a medical expense insurance. Such dialysis medical expenses will tend to be increasing from now on.

[0022]

Hepatic coma in hepatic failure patients is caused by decrease in activity of urea cycle of the liver. Also, ammonia escalated in the blood due to the hepatic failure has a bearing on the circulation cycle of the intestine and blood. As a medical formula for discharging the ammonia to the outside of the body, there has been recognized a dose of chemical absorbing agent such as activated charcoal and cation-exchange resin is effective as a medical supply. However, heavy dosage of the absorbing agent having a possible side effect places an enormous burden to the patient. Under the circumstances, a need has been felt for an effective solution capable of reducing the burdens involved in treating.

[0023]

Thus, the present invention seeks to provide a superior solution of the aforementioned problems involved in treating a patient with kidney failure or hepatic failure.

[0024]

#### (DISCLOSURE OF THE INVENTION )

The inventors of this invention has found the solution for attaining the objects described above, by administering indigestible polysaccharides as food having energy required for protein synthesis by bacteria, which is difficult to digest according to digestive enzyme and may be ingested as food according to intestinal bacteria, for the purpose of making use of low-molecular-weight nitrogen-containing compounds that are drained into the intestine and circulated in the reingested state as ingredients for fungal protein synthesis of intestinal bacteria to reduce the financial and temporal burdens involved in undergoing the hemodialysis treatment without taking any drug medicines having potential adverse effects. This invention could be achieved on the strength of this biochemical knowledge.

[0025]

That is, the present invention provides pathological improvement food composed chiefly of indigestible polysaccharides and having restricted addition of protein components, which contains trace metal, vitamin and/or fat as required.

[0026]

## (A MODE FOR CARRYING OUT THE INVENTION )

The invention will be described hereinafter in detail.

[0027]

The aforementioned indigestible polysaccharides include pectine, that is in an apple, strawberry and citrus, seaweed-derived alginic acid, fucoidan, crustacean chitin, chitosan, gums such as acacia gum, arum root-derived mannan, agar, polydextrose that is glucose polymer, test-derived water-soluble dietary fiber (hemicellulose) such as corn, soybeans and psyllium, and sugar alcohol and polymers of sugar alcohol.

[0028]

Of the aforesaid substances, the pectine can easily be made from an apple or citrus fruit or obtained as a co-product in the making of citrus drinks. There can be produced alginic acid and fucoidan from seaweeds, and the chitin and chitosan from crustacean shells with simple operation. The polydextrose can be made by polymerizing a natural product such as glucose as a basic ingredient in the presence of citric acid. A variety of testa-derived water-soluble dietary fibers are commercially available.

[0029]

The pathological improvement food according to the invention contains more than 50% by weight of indigestible polysaccharide as a chief ingredient relative to the solid content of the food in terms of dried foodstuff.

[0030]

The proportion of the protein component (i.e. protein and its partially hydrolyzed protein (peptide)) to the solid content is made to 2% or less by weight in terms of dried foodstuff.

[0031]

The indigestible polysaccharides according to the invention contains, as basic ingredients, singly the aforementioned indigestible polysaccharides or compounds combined with several kinds of indigestible polysaccharides controlled in sweetness and acerbity with sweetener such as sucrose, fructose, glucose and sugar alcohol or natural sweetener such as luohan fruit essence and citric acid. To strengthen the effect of a dietary supplement, the indigestible polysaccharides of the invention may additionally contain sodium salt, potassium salt, magnesium salt and calcium salt, and further the needed volume of trace metals such as Zn, Fe, Cu, Co, Mn, Cr and Se in the form of the approved food additives. To further strengthen the effect of the dietary supplement, the indigestible polysaccharides of the invention may additionally contain, as a primary body, substances fortified with a suitable quantity of vitamins such as vitamin A, vitamin B family (e.g. B1, B2, B6, B12 and nicotine acid), vitamin C, Vitamin E, and folic acid, essential fatty acid or omega-3 fat. The indigestible polysaccharides of the invention may be produced in the form of a liquid (drink), jelly or cream or in a solid or semisolid form like a biscuit, cookie, bread, noodles, cake, ice cream, and sherbet and can be given singly or in combination to a patient with kidney failure or hepatic failure.

[0032]

It may be preferably to make a variety of the indigestible polysaccharides according to the invention with variations so as to keep the patient from being bored by being flavored with fruit juice such as of an apple, lemon, strawberry, blueberry, mandarin orange, orange, pomegranate, litchee, pineapple, papaya and banana, or flavoring agents.

[0033]

Through experiments using pigs, it has been actually demonstrated the fact that the indigestible polysaccharides of the invention have a significant effect of reducing urinary excretion of nitrogen-containing low-molecular substances and excreting almost all the ingested nitrogen into feces (Lecture Abstract of 76th Meeting of The Japanese Society of Swine Science; Lecturers: Yamamoto et al., The Japanese Journal of Swine Science, Vol. 38 (4), p. 227 (2001)). Yamamoto et al. announced in the meeting that urinary urea excretion was decreased to one-tenth when raise healthy pigs for seven days with a feed of low-protein feeding stuff (nitrogen intake 35.5 grams per day on an average) mixed with 30% by weight of apple juice lees (dried foodstuff). The nitrogen equivalent to the substance taken up by feces could be retrieved.

[0034]

The experimental results using the pigs support the possibility that the diet containing indigestible polysaccharides brings about significant effects of lowering the concentration of nitrogen-containing low-molecular substances in the blood of a hepatic failure patient so as to hold over treatments with hemodialysis or reduce the number of treatments with hemodialysis, or lowering the concentration of blood

ammonia level of a kidney failure patient to prevent hepatic coma. However, the experimental results using the pigs do not always indicate the effectiveness of the pathological improvement food of the invention in treating the patients with kidney failure and hepatic failure from the viewpoint of the dose of the indigestible polysaccharides applied to the pigs for experimental purpose.

[0035]

To put it another way, the pathological improvement food of the invention, which chiefly contains indigestible polysaccharides, can take various forms such as drink, cream, biscuit, bread, cake, ice cream and provide various textures by diversely combining different kinds of indigestible polysaccharides or determining the amount of each ingredient, or the pathological improvement food of the invention may be made in the form of powder composed of required ingredients. Therefore, desirable diet food as mentioned above may be made in the home according to the patients' predilection and used as recipe ingredients.

[0036]

The typical of indigestible polysaccharides is pectine. The pectine is contained in plenty in an apple and citrus fruit and remains in existence in high concentration in fruit juice lees. Thus, the pectine can be extracted from the lees and processed into a dry product upon being de-esterified with acid or alkali and purified. It may also be processed into a dry product upon being de-esterified with acid or alkali and purified. It may also be processed in such a manner of being extracted from the apple, pericarp of citrus fruit or vegetable, de-esterified with acid or alkali, filtrated, concentrated, precipitated with alcohol to be cleansed, dried and broken



into powder. The pectine may be taken out by being refined for use in this invention in the manner described above, but apple juice lees or fruit juice lees of citrus fruit (mandarin orange, orange, grapefruit, etc.) may be used as they are for the same purpose as the refined pectine because these juice lees are rich in pectine. That is, the pectine termed in this invention includes the apple juice lees or citrus fruit juice lees. Likewise, alginic acids and fucoidan, which are made from seaweed, and polydextrose made from glucose as a basic ingredient in the presence of citric acid can be used as the indigestible polysaccharide. These indigestible polysaccharides for use in the invention should not necessarily be understood as being limited to the refined products as long as the effect of the invention is not ruined.

[0037]

The polysaccharide becomes viscous when dissolving in water because it can absorb large volume of water into its polymer structure. Therefore, when the indigestible polysaccharide is used in the preparation of a beverage, the concentration thereof is desirably 0.5% to 30% by weight. Also, it is preferable to determine the concentration of the same 2% to 30% by weight for creamy food, 2% to 30% by weight for jellylike food, and 5% to 60% by weight for cakes, and 5% to 60% by weight for dried foods such as biscuits.

[0038]

A patient with kidney failure or hepatic failure often lacks ingestion of trace metals, which are considered to be fundamental to maintenance of physical functioning, such as Mg, Zn, Fe, Co, Mn, Cr and Se due to unbalanced diet. Likewise, a patient undergoing hemodialysis treatment often lacks ingestion of the trace metals

due to exteriorize thereof during hemodialysis, consequently to possibly cause renal anemia.

[0039]

The pathological improvement food of the invention may contain 0.01% to 5.0% by weight of trace metals in a free state or in the additive form of metal-containing yeast (e.g. "Mineral Yeast" made by Oriental Yeast Co., Ltd.). The pathological improvement food thus produced even containing such trace metals does not have a disagreeable smell endemic to metal nor nasty taste and can be made in safety.

[0040]

The present invention provides effective means capable of decreasing the amount of nitrogen reabsorbed from the intestine into the bloodstream to suppress the rise of concentration of the low-molecular-weight nitrogen-containing compounds in the blood through the exquisite biodynamic mechanism in which the low-molecular-weight nitrogen-containing compounds such as urea discharged from the blood (through the blood vessel) into the intestine are effected for protein synthesis of intestinal bacteria and passed out with feces. To accomplish the intended means, the food prepared with the indigestible polysaccharide, which is not easily exploited by digestive enzyme but is effective for the intestinal bacteria, thereby to make use of its resultant energy for protein synthesis of intestinal bacteria.

[0041]

Intrinsically, the low-molecular-weight nitrogen-containing compounds in the blood such as urea and ammonia are secreted into the intestine with the bodily fluid and reabsorbed, thus being circulated between the fluid in the intestine and the blood. Therefore, the nitrogen-containing low-molecular substances secreted into the intestine can be utilized as a nitrogen source working on the protein synthesis of intestinal bacteria and discharged to the outside of the body as feces upon proliferating the fungus bodies, thereby to break off the circulation of nitrogen-containing compounds between the intestine and the blood, resulting in a lower concentration in the blood. Thus, the excretion of the compounds effects alleviating of a burden on the kidney.

[0042]

The reduced burden of the kidney causes degeneration of kidney glomerulus to be retarded, so as to have an expectancy to retard a transition to hemodialysis treatment and decrease the number of hemodialysis.

[0043]

If a kidney failure patient periodically takes the pathological improvement food of the invention after each meal and/or between meals, a part of the low-molecular-weight nitrogen-containing compound in the blood is partially converted into intestinal bacterial protein and then excreted as feces, resulting in lowering of the blood concentration thereof, so as to enable the transition to hemodialysis treatment to be retarded and the number of required hemodialysis to be decreased. As a result, the various problems posed by the hemodialysis treatment can effectively be solved, consequently to heighten the quality of life of the patient.

[0044]

Also, when the pathological improvement food having the function of driving the fungal protein synthesis of intestinal bacteria with ammonia secreted into the intestine and excreting the ammonia with feces is given to a patient with hepatic failure after each meal and/or between meals, the problems as above can be solved, so that distress involved in taking high doses of adsorbent agent can be relieved without producing any side effect according to the invention.

[0045]

The nitrogen-containing compound, specifically ammonia, in the urine, emits urine odor, whereas the urine odor given out due to anesthesia excretion of a bedridden patient or elderly person can be diminished.

[0046]

(Embodiment 1: Beverage )

[0047]

Table 1 below shows solid contents of the essential constituent parts of the pathological improvement food of the invention per 100 grams of beverage made by adding water to the essential constituents. There was prepared 100 grams of beverage (product) by adding water thereto.

[0048]

TABLE 1

Basic Ingredients	Solid contents per 100 grams of beverage
Polydextrose	~20 g
Pectine	~20 g
Fructose	~5 g
Citric acid - Na	~400 mg
Vitamin C	~500 mg
Vitamin B <sub>1</sub>	~20 mg
Vitamin B <sub>2</sub>	~20 mg
Vitamin B <sub>6</sub>	~2 mg
Vitamin B <sub>12</sub>	~1 mg
Nicotinic-acid amide	~20 mg
Folic acid	~5 mg
DHA	~0.5 mg
Calcium glycerophosphate	~300 mg
MgCl <sub>2</sub>	~200 mg
Fe-containing mineral yeast	~30 mg
Zn-containing mineral yeast	~50 mg
Cu-containing mineral yeast	~30 mg
Mn-containing mineral yeast	~10 mg
Arum root powder or Agar	q.s.
Food flavor (of apple, citrus and so on)	q.s.
Fruit juice or fruit essence	q.s.
Texture improving agent	q.s.
Sweetener	q.s.

Water is added to define the total as 100.

pH: 4.5 to 5.5/Viscosity: 50 to 500 mPas

Color: Light yellow-light brown/Taste: Moderately adjusted with sweet and acid

Energy: 30 to 80 kcal/100 g

Mineral Yeast: Cr- or Se-containing mineral yeast may be added arbitrarily.

[0049]

Table 1 exemplifies the daily intake of the beverage. The beverage may be taken in daily after each meal during dialysis treatment at one time or in divided doses.

Alternatively, it may be drunk with food items described in Embodiment 2 and

Embodiment 3 in combination. The daily intake as exemplified herein may of course be increased.

[0050]

Apple juice lees can be substituted for pectine.

[0051]

Fructose may be replaced with one of sucrose, sugar alcohol and other sweeteners or a mixture of these. As the sweetener, there may also be used natural sweetener such as luohan fruit essence, stevia, licorice extract. An artificial sweetener such as Aspartame may be used.

[0052]

For improving the texture of the pathological improvement food, 0.1 to 3 grams of agar powder or alimant arum root powder may be added to make the food jelly.

[0053]

When drinking 200 to 300 grams (equivalent in solid content) of the beverage thus prepared a day, 4 to 8 grams of protein taken on the same day are fixed into intestinal bacterial protein, consequently to be excreted with feces. As a result, the blood concentration of low-molecular-weight nitrogen-containing compounds such as urea can be decreased corresponding to the amount of nitrogen content in the fungal protein, to alleviate a burden on the kidney.

[0054]

The conditions at that time can be formulated by the following formula.

[0055]

That is, there can be proved experimentally the following relation in which the intestinal bacteria gains energy by exploiting indigestible polysaccharides using, as a nitrogen source, low-molecular-weight nitrogen-containing compounds such as urea secreted in the intestine in fungal protein synthesis.

[0056]

(a) Assuming that the total energy content of indigestible polysaccharide is generally 3.6 kcal/g and 50% of the energy is consumed by the fungus body, the energy at which the indigestible polysaccharide ( $A_g$ ) are consumed by the fungus body is  $A_g \times 3.6 \text{ kcal/g} \times 0.5 = 1.8 \times A$  (kcal).

[0057]

(b) Assuming that the energy required for fungal protein synthesis is generally 5.66 kcal/g protein and the energy use efficiency by the intestinal bacteria is 44%, the fungal protein synthesis of  $B_g$  necessitates  $B_g \times 5.66 \text{ kcal} \times 0.44 = 12.8 \times B$  (kcal). Accordingly, the approximate amount of bacterial protein ( $B_g$ ) synthesized by oral administration of the indigestible polysaccharide of  $A_g$  is  $1.8 \times A / 12.8$ .

[0058]

(c) When taking 300 g of beverage of Embodiment 1 noted above a day, it corresponds to the intake (A) of 30 to 60 grams of the indigestible polysaccharides, and the fungal protein content (B) synthesized at that time becomes 4.2 to 8.4 grams.

[0059]

When a kidney failure patient (50 kg body weight) consumes 30 grams of protein a day (0.6 g/kg body weight), the intake of 300 grams of the beverage in terms of solid content brings about the same effect as intake reduction by 4% to 17% of protein.

[0060]

(Embodiment 2: Jellylike Food )

Table 2 below shows parts of the essential constituents of the jellylike food.

[0061]

TABLE 2

Basic Ingredients	Blending Quantity
Apple juice lees	3 to 20 g
Pectine	1 to 10 g
Polydextrose	10 to 20 g
Arum root-derived mannan	0.1 to 2 g

Water is added to be 60 to 105 grams.

[0062]

Fructose, citric acid, sodium citrate, vitamin C, vitamin B family (B1, B2, B6, nicotinic-acid amide, and B12), trace metals, and mineral yeast all are contained in a similar manner in the beverage (former embodiment) and the jellylike food. Thus, the jellylike food can be produced by adding fructose and the subsequent ingredients shown in Table 1 to three ingredients shown in Table 2. The water content of the food is regulated by adding water to the food so as to make a total of 60 to 105 grams in total.



[0063]

The jellylike food prepared in the aforementioned manner may be stored in containers of, for example, 20, 25 or 35 grams in a sterile condition. It may of course be contained in a larger container or packager.

[0064]

The aforesaid jellylike food (20-gram, 25-gram or 35-gram package) may be taken after each meal or during dialysis treatment as needed. When consuming one dose of food of the quantity described above three times a day, the daily intake of indigestible polysaccharides becomes roughly 25 grams (20-gram package) to 40 grams (35-gram package), so that 3.5 grams/day (20-gram package) to 6.3 grams/day (35-gram package) of protein ingested from the food on the day are fixed onto the intestinal bacterial protein and excreted into feces.

[0065]

Even if the protein intake (or nitrogen intake) fluctuates from day to day, it is equivalent to the total excretion amount of nitrogen. The intake of indigestible polysaccharides enhances the effect of introducing the nitrogen into feces via the principal excreting route rather than feces routed through the kidney or large intestine, thereby to lessen a burden imposed on the kidney and bring about an effect of detoxication and exclusion of nitrogen-containing compounds such as urea secreted into the intestine.

[0066]

Incidentally, a hepatic failure patient may possibly be relieved from the sufferings from gastrointestinal disorder such as diarrhea due to ammonia secreted into the intestine.

[0067]

(Embodiment 3 :Confectionery such as Biscuits or Cookies )

Dry or semidry products such as cookies, biscuits bread or rice crackers may be produced by using indigestible polysaccharides as a chief constituent. The composition of the chief constituent of food will be shown in Table 3 below.

[0068]

TABLE 3

Basic Ingredients	% (Dry weight)
Polydextrose	5 to 25%
Apple juice lees	10 to 40%
Pectine	3 to 15%
Cellulose fiber	5 to 10%
Oligosaccharide	15 to 30%
Starch (Low-gluten wheat)	5 to 20%
Butter (or Shortening)	10 to 20%
Others(*)	1 to 10%

(\*)1% to 10% of sweetener, food flavor, vitamins and minerals are added on the basis of Embodiments 1 and 2.

[0069]

As cellulose fiber, microscopic cellulose powder such as "SolcaFloc 300FCC" (Danisco Japan KK) may be used by way of example. As the starch, potato starch,

corn starch, kudzu starch, and low-gluten wheat, which are is low in protein, may be preferably used. Soft wheat flour may be used within the realm of using the starch.

[0070]

When taking six articles of food (e.g. cookies) made from the ingredients described above every day, the intake of indigestible polysaccharides is about 30 to 50 grams. As a result, 4 to 6 grams of dietary protein are bypassed through the fecal route.

[0071]

The food products such as the beverage, jelly and cookies shown in Embodiments 1, 2 and 3 may be taken singly or in combination so as to excrete substantial amount of dietary-derived nitrogen components with urine and feces. The combination of the pathological improvement food of the invention and regular meals including clinical diet brings about a noticeable synergistic effect with ease.

[0072]

When taking 100 grams of beverage (solid content equivalent), two packages of jelly (25 grams per package), and six cookies by mixture daily in several divided intakes, fungal protein synthesis runs to 10 to 15 grams, resulting in excretion of the low-molecular-weight nitrogen-containing compounds corresponding to equal parts of the fungal protein synthesis through a defecation route, not through a micturition route.

[0073]

#### (Embodiment 4: Test for Improvement of Clinical Conditions (Case 1) )

Three packages of jelly-like food (25 grams each) as described in Embodiment 2 and six cookies as described in Embodiment 3 were given to four healthy male volunteer subjects and four healthy female volunteer subjects (eight subjects in total) a day. The total quantity of indigestible polysaccharides was 80 grams per day on average, and the daily protein intake was 0.6 g/kg body weight.

[0074]

The experimental subjects were divided into two groups by gender and subjected to a cross-over method. To be specific, two male and two female subjects in one group started eating control diet food at the outset of the dietary test and took experimental diet food from the 5th day, and then, continued to eat the experimental diet food for 4 days. The other group composed of two male and two female subjects started eating the experimental diet food and took and continued to each control diet food from the 5th day for 4 days.

[0075]

An explanation about the objectives of the dietary test, the compositions of the food under test and safety of the food was made to the experimental subjects to gain their consent in writing.

[0076]

Blood samples of the subjects were taken in the morning fasting to measure BUN, and all urine of the respective subjects was collected to provide measurement

for urinary nitrogen every day. The experimental results obtained eventually are shown in Table 4 below.

[0077][0078]

As shown in Table 4, the excretion amount of nitrogen into the urine was decreased by 34% and BUN is improved by 30%.

[0079]

(Embodiment 5: Test for Improvement of Clinical Conditions (Case 2) )

An experiment on the influence of the pathological improvement food on nitrogen excreted into the feces, BUN, urinary urea and ammonia was conducted by giving three jelly-like food products (25 grams each) as shown in Embodiment 2 a day and six cookie-like food products in two to three divided doses a day.

[0080]

From kidney failure patients who need not hemodialysis, but have higher BUN and have habitually kidney-supporting diets, five experimental subjects were selected with the written consent of the patients upon explaining the research purposes, prescribed diet food and schedule of experiment. The experiment was conducted by collecting blood samples from the patients at the same time each day to measure BUN and collecting all urine from the respective patients to measure the amounts of urea and ammonia every day. All feces of the respective patients were collected on the 7th, 8th and 9th days during the test to measure the total nitrogen amounts. On 7th, 8th and 9th days, the same meals were prepared, and the total

amount of nitrogen of each meal and the intake of nitrogen were calculated. The calculated amounts thereof are shown in Table 5 below.

[0081]

TABLE 5

		<u>(1) Feces</u>					
		Test period					
		Control period for non-dose			Period for dose		
		Lapsed days					
		7	8	9	7	8	9
Fecal amount		95.2 ± 32.8	98.5 ± 29.1	103.8 ± 43.7	93.7 ± 28.3	102.9 ± 40.2	126.1 ± 53.2
Total nitrogen amount (g/day)		1.9 ± 0.45	2.0 ± 0.21	2.1 ± 0.28	2.50 ± 0.50	2.62 ± 0.45	2.80 ± 0.23

		<u>(2) Blood and Urine</u>									
		Test period									
		Control period for non-dose					Period for dose				
		Lapsed days									
		1	4	7	10	14	2	4	7	10	14
Blood	BUN (mg/dl)	35.3	36.2	33.7	34.6	34.8	30.8	28.3	26.1	25.3	24.8
Urine	Volume (L/day)	1.51	1.39	1.46	1.53	1.48	1.43	1.56	1.38	1.52	1.48
	Total nitrogen (g/day)	3.7	3.9	3.9	3.4	3.6	3.2	2.8	2.8	2.4	2.6

[0082]

As seen from Table 5, increase in amount of the feces and nitrogen excreted into the feces was confirmed on 9th day of a course of the experiment by the possible cause considered to be formula of the sample diet food. It was also confirmed that BUN was decreased by 20% and the excretion amount of nitrogen into the urine was improved by 30% to 60% on a daily basis.

[0083]

(Embodiment 6: Test for Improvement of Clinical Conditions (Case 3) )

From patients undergoing dialysis three times a week, five experimental subjects were selected with the written consent of the patients upon explaining the research purposes, prescribed diet food and schedule of experiment in the same manner as in Embodiment 6. The experiment was conducted by giving the same diet food of the same amount as supplied in Embodiment 6 to the patients, to measure the total amount of nitrogen excreted into the feces and BUN. The results are shown in Table 6 below.

[0084]

TABEL 6

	Test period					
	Control period for non-dose			Period for dose		
	Lapsed days					
	7	8	9	7	8	9
Fecal amount	75.8 ± 22.8	81.3 ± 29.1	78.8 ± 43.7	73.7 ± 22.3	82.9 ± 30.2	86.1 ± 53.2
Total nitrogen amount (g/day)	1.30 ± 12	1.43 ± 23	1.35 ± 18	1.49 ± 29	1.62 ± 26	1.57 ± 35
BUN (mg/dl)	48.5	53.2	46.6	34.8	37.3	32.4

[0085]

As seen from Table 6, increase in amount of the feces and nitrogen excreted into the feces was confirmed on 9th day of a course of the experiment by the possible cause considered to be formula of the sample diet food. It was also

confirmed that BUN was decreased by about 30% on the 9th day and significant improvement occurred.

[0086]

(Effect of the invention)

The pathological improvement food according to the invention has a function of decreasing reabsorption of low-molecular-weight nitrogen-containing compounds such as urea circulating in the blood and intestine and then excreting the nitrogen-containing compounds in the form of feces through the mechanism of using nitrogen of ingested protein as an agent for fungal protein synthesis of intestinal bacteria. Accordingly, the pathological improvement food of the invention brings about the following effects.

[0087]

(1) The blood concentration of the nitrogen-containing low-molecular substances such as BUN and ammonia can be lowered. (2) It becomes possible to alleviate the burdens exerted on the kidney of a kidney failure patient and retard a transition to hemodialysis treatment only by taking a specified quantity of the food of the invention every day. (3) The number of required hemodialysis required for treating kidney failure can be decreased to lessen the psychological, temporal and financial burdens upon the patient and heighten the quality of life of the patient while saving medical expenses. (4) The blood ammonia level can be decreased so as to keep a patient with acute or chronic hepatic failure from a danger of falling into hepatic coma and improve the medical condition of the patient.



## Abstract

Food for improving clinical conditions capable of lowering the concentration of low-molecular weight nitrogen-containing compounds in blood

The present invention aims at preventing or retarding a transition to hemodialysis treatment in kidney failure or decreasing the number of implementation of the hemodialysis therapy and preventing or lessening occurrence of accompanying hyperammonemia in hepatic insufficiency. To accomplish the purposes described above, the pathological improvement food of the invention is featured by being composed chiefly of indigestible polysaccharides and having restricted addition of protein components. Energy produced by exploiting the indigestible polysaccharides contributes to fungal protein synthesis using, as a N-source, urea or ammonia secretion into the intestine and excretion of proliferated bacteria with feces, so that nitrogen-containing low-molecular substances in the blood can be decreased, thereby to improve disorder of the kidney and liver.